

**Experiment Number:** R92025B  
**Test Type:** RACB  
**Route:** Dosing in Feed  
**Species/Strain:** Rat/Sprague-Dawley

**PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence**  
**Test Compound:** 4-Methylimidazole  
**CAS Number:** 822-36-6

**Date Report Requested:** 09/04/2018  
**Time Report Requested:** 09:32:54  
**Lab:** RTI

**C Number:** R92025B  
**Study Gender:** Both  
**PWG Approval Date** See web page for date of PWG Approval

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	F0 Male			
	Treatment Groups (ppm)			
	0	750	2500	5000
<b>Disposition Summary</b>				
Animals Initially In Study	23	23	23	23
Early Deaths				
Unscheduled Sacrifice			3	2
Survivors				
Scheduled sacrifice, terminal (SD 15 - 178)	23	23	20	21
Number of Animals Examined	23	23	23	23
<b>ALIMENTARY SYSTEM</b>				
LIVER	(23)	(0)	(23)	(23)
BASOPHILIC FOCUS			1 (4.3%)	
CLEAR CELL FOCUS			3 (13%)	
HEPATODIAPHRAGMATIC NODULE			1 (4.3%)	
PERIPORTAL; LYMPHOCYTE; INFILTRATION; FOCAL			2 (8.7%)	
INFLAMMATION, CHRONIC; ACTIVE, FOCAL			1 (4.3%)	
CENTRIOBULAR; NECROSIS; DIFFUSE			1 (4.3%)	
CENTRIOBULAR; NECROSIS; FOCAL			1 (4.3%)	
CENTRIOBULAR; HEPATOCYTE; VACUOLATION; CYTOPLASMIC	0 **			19 (82.6%) **
<b>CARDIOVASCULAR SYSTEM</b>				
None				

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Lab: RTI

Species/Strain: Rat/Sprague-Dawley

## F0 Male

## Treatment Groups (ppm)

	0	750	2500	5000
<b>ENDOCRINE SYSTEM</b>				
ADRENAL GLANDS	(23)	(0)	(23)	(23)
CORTEX; HYPERTROPHY; FOCAL	0 *			3 (13%)
CORTEX; BILATERAL; VACUOLATION; DIFFUSE	3 (13%)		3 (13%)	
CORTEX; VACUOLATION; FOCAL	1 (4.3%) *		1 (4.3%)	5 (21.7%)
PITUITARY GLAND	(23)	(0)	(23)	(23)
PARS DISTALIS; CYST				1 (4.3%)
THYROID GLANDS	(23)	(0)	(23)	(23)
C-CELL; HYPERPLASIA; FOCAL	1 (4.3%)			
<b>GENERAL BODY SYSTEM</b>				
None				
<b>GENITAL SYSTEM</b>				
COWPERS GLANDS	(23)	(0)	(20)	(21)
UNILATERAL; ATROPHY	1 (4.3%)			
EPIDIDYMIS	(22)	(23)	(23)	(23)
DUCT; EXFOLIATED GERM CELL (TOTAL)	1 (4.5%) **		3 (13%)	7 (30.4%) *
HYOSPERMIA			1 (4.3%)	
PROSTATE	(23)	(23)	(23)	(23)
VENTRAL LOBE; ATROPHY	0 **	9 (39.1%) **	20 (87%) **	23 (100%) **
VENTRAL LOBE, INTERSTITIUM; LYMPHOCYTE; INFILTRATION	5 (21.7%) **	5 (21.7%)	1 (4.3%)	0 *
VENTRAL LOBE; INFLAMMATION; CHRONIC ACTIVE		1 (4.3%)		
TESTIS	(22)	(23)	(23)	(23)
GERMINAL EPITHELIUM; ATROPHY				1 (4.3%)
GERM CELL; DEGENERATION	1 (4.5%) **		4 (17.4%)	8 (34.8%) *
SEMIFEROUS TUBULE; SPERMATID RETENTION (TOTAL)	2 (9.1%) *	3 (13%)	1 (4.3%)	8 (34.8%) *

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	<b>F0 Male</b>			
	<b>Treatment Groups (ppm)</b>			
	<b>0</b>	<b>750</b>	<b>2500</b>	<b>5000</b>
<b>HEMATOPOIETIC SYSTEM</b>				
None				
<b>INTEGUMENTARY SYSTEM</b>				
None				
<b>LYMPHOID SYSTEM</b>				
None				
<b>MUSCULOSKELETAL SYSTEM</b>				
None				
<b>NERVOUS SYSTEM</b>				
None				
<b>RESPIRATORY SYSTEM</b>				
None				
<b>SPECIAL SENSES SYSTEM</b>				
None				
<b>URINARY SYSTEM</b>				
KIDNEYS	(23)	(0)	(23)	(23)
PELVIS; CONCRETION; FOCAL			1 (4.3%)	
NEPHROPATHY, CHRONIC PROGRESSIVE	22 (95.7%)		19 (82.6%)	22 (95.7%)

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F0 Female				
	Treatment Groups (ppm)			
	0	750	2500	5000
<b>Disposition Summary</b>				
Animals Initially In Study	23	23	23	23
<b>Early Deaths</b>				
Euthanized, moribund	1	1	3	8
Found Dead			1	1
Unscheduled Sacrifice				2
<b>Survivors</b>				
Scheduled sacrifice, terminal (LD 4, SD 28 - 220)	22	22	19	12
Number of Animals Examined	23	10	23	23
<b>ALIMENTARY SYSTEM</b>				
LIVER	(23)	(3)	(23)	(23)
ATROPHY; DIFFUSE				2 (8.7%)
CONGESTION; DIFFUSE	1 (4.3%)			1 (4.3%)
DEFORMITY		1 (33.3%)		
HEMATOPOIESIS; EXTRAMEDULLARY, FOCAL			1 (4.3%)	2 (8.7%)
HEPATODIAPHRAGMATIC NODULE		1 (33.3%)		
PERIPORTAL; LYMPHOCYTE; INFILTRATION; FOCAL	2 (8.7%)		1 (4.3%)	2 (8.7%)
CENTRIOBULAR; NECROSIS; DIFFUSE				1 (4.3%)
CENTRIOBULAR; NECROSIS; FOCAL			1 (4.3%)	
<b>CARDIOVASCULAR SYSTEM</b>				
None				

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**F0 Female**

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**Treatment Groups (ppm)**

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**0**

**750**

**2500**

**5000**

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**ENDOCRINE SYSTEM**

ADRENAL GLANDS	(23)	(1)	(23)	(23)
CONGESTION; DIFFUSE			1 (4.3%)	
CORTEX; HYPERTROPHY; FOCAL				2 (8.7%)
CORTEX; VACUOLATION; FOCAL	3 (13%)			3 (13%)
PITUITARY GLAND	(23)	(1)	(23)	(23)
PARS DISTALIS; CYST				2 (8.7%)
THYROID GLANDS	(23)	(1)	(23)	(23)
C-CELL; HYPERPLASIA; FOCAL	0 *			3 (13%)

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**GENERAL BODY SYSTEM**

None

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Route: Dosing in Feed

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Lab: RTI

Species/Strain: Rat/Sprague-Dawley

F0 Female

Treatment Groups (ppm)

	0	750	2500	5000
<b>GENITAL SYSTEM</b>				
CERVIX	(23)	(1)	(23)	(21)
INFLAMMATION; ACUTE			1 (4.3%)	
CLITORAL GLANDS	(3)	(4)	(1)	(1)
UNILATERAL; ABSCESS; CHRONIC			1 (100%)	
DUCT; ECTASIA (TOTAL)	2 (66.7%)	4 (100%)		1 (100%)
INFILTRATION; MONONUCLEAR CELL	1 (33.3%)			1 (100%)
DUCT; LUMEN; INFLAMMATION, ACUTE				1 (100%)
INFLAMMATION, CHRONIC; ACTIVE (TOTAL)		3 (75%)		
OVARIES	(23)	(1)	(23)	(23)
CONGESTION	1 (4.3%)			
CORPUS LUTEUM; CYST				2 (8.7%)
FOLLICLE; CYST				1 (4.3%)
PLACENTA	(0)	(0)	(1)	(5)
BILATERAL; EDEMA				1 (20%)
EDEMA; DIFFUSE				3 (60%)
EDEMA				1 (20%)
INFLAMMATION; ACUTE				1 (20%)
INFLAMMATION; SUPPURATIVE				1 (20%)
NECROSIS; BILATERAL DIFFUSE				1 (20%)
NECROSIS; DIFFUSE				1 (20%)
NECROSIS				1 (20%)
UTERUS	(23)	(3)	(23)	(23)
ENDOMETRIUM; CYST				1 (4.3%)
OVIDUCT; CYST			1 (4.3%)	
DILATION (TOTAL)		1 (33.3%)	1 (4.3%)	
ENDOMETRIUM; HYPERPLASIA; CYSTIC	2 (8.7%)			4 (17.4%)
INFLAMMATION; CHRONIC-ACTIVE			1 (4.3%)	

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	F0 Female			
	Treatment Groups (ppm)			
	0	750	2500	5000
INFLAMMATION; SUPPURATIVE ENDOMETRIUM; METAPLASIA; SQUAMOUS (TOTAL) NECROSIS	2 (8.7%)	1 (33.3%)		2 (8.7%)
ULCER; MULTIFOCAL VAGINA CYST	(23)	(1)	1 (4.3%) (23)	1 (4.3%) (23)
SUBMUCOSA; LYMPHOCYTE; INFILTRATION; FOCAL INFLAMMATION; ACUTE MUCIFICATION ULCER; FOCAL	1 (4.3%)		1 (4.3%) 5 (21.7%) 1 (4.3%)	0 **
<b>HEMATOPOIETIC SYSTEM</b>				
THYMUS CORTEX; DECREASED LYMPHOCYTE; DIFFUSE	(23) 0 **	(1)	(22) 2 (9.1%)	(23) 6 (26.1%) **
<b>INTEGUMENTARY SYSTEM</b>				
MAMMARY GLANDS INFILTRATION; BACTERIA INFLAMMATION; SUPPURATIVE	(1) 1 (100%) 1 (100%)	(2)	(0)	(0)
<b>LYMPHOID SYSTEM</b>				
None				
<b>MUSCULOSKELETAL SYSTEM</b>				
BONE INTERVERTEBRAL DISK; RUPTURE; FOCAL	(1) 1 (100%)	(0)	(0)	(0)
<b>NERVOUS SYSTEM</b>				
None				



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**F0 Female**

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**Treatment Groups (ppm)**

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**0**                      **750**                      **2500**                      **5000**

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**RESPIRATORY SYSTEM**

None

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**SPECIAL SENSES SYSTEM**

None

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**URINARY SYSTEM**

	0	750	2500	5000
KIDNEYS	(23)	(1)	(23)	(23)
PELVIS; CONCRETION; FOCAL PAPILLA; COLLECTING DUCT; DILATION INFLAMMATION, ACUTE; FOCAL	1 (4.3%)			1 (4.3%)
MINERAL	1 (4.3%)		2 (8.7%)	1 (4.3%)
RENAL TUBULE; NECROSIS; ACUTE, MULTIFOCAL	0 *			3 (13%)
NEPHROPATHY, CHRONIC PROGRESSIVE	17 (73.9%)	1 (100%)	11 (47.8%)	11 (47.8%)

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F1 Male : F1 NonParental Male

	Treatment Groups (ppm)		
	0	750	2500
<b>Disposition Summary</b>			
Animals Initially In Study	49	56	20
Early Deaths			
Survivors			
Scheduled sacrifice, terminal (PND 91 - 93)	49	56	20
Number of Animals Examined	49	56	20
Total number litters	18	22	8
<b>ALIMENTARY SYSTEM</b>			
LIVER	(49)	(1)	(20)
DEFORMITY			1 (5%) [1]
HEMATOPOIETIC CELL PROLIFERATION; EXTRAMEDULLARY			1 (5%) [1]
HYPERTROPHY; HEPATOCELLULAR	3 (6.1%) [2]		
ACCESSORY LOBE; INFARCTION		1 (100%) [1]	
LYMPHOCYTE; INFILTRATION; MULTIFOCAL	1 (2%) [1]		
<b>CARDIOVASCULAR SYSTEM</b>			
None			
<b>ENDOCRINE SYSTEM</b>			
ADRENAL GLANDS	(49)	(1)	(20)
ATROPHY; DIFFUSE		1 (100%) [1]	
CORTEX; HYPERTROPHY; FOCAL	2 (4.1%) [1]		
METAPLASIA; OSSEOUS			1 (5%) [1]
CORTEX; VACUOLATION; FOCAL	1 (2%) [1]		
PITUITARY GLAND	(49)	(0)	(20)
PARS DISTALIS; CYST	4 (8.2%) [3]		

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Lab: RTI

F1 Male : F1 NonParental Male

Treatment Groups (ppm)

0

750

2500

GENERAL BODY SYSTEM

None

GENITAL SYSTEM

EPIDIDYMIS

(49)

(56)

(20)

DUCT; EXFOLIATED GERM CELL

3 (6.1%) [2]

5 (8.9%) [4]

4 (20%) [4]

PROSTATE

(49)

(56)

(20)

VENTRAL LOBE; ATROPHY

4 (8.2%) [3] \*\*

25 (44.6%) [17] \*\*

17 (85%) [7] \*\*

VENTRAL LOBE, INTERSTITIUM; LYMPHOCYTE; INFILTRATION

25 (51%) [13]

33 (58.9%) [18]

6 (30%) [5]

VENTRAL LOBE; INFLAMMATION; CHRONIC ACTIVE

1 (2%) [1]

INFLAMMATION; CHRONIC ACTIVE

1 (2%) [1]

SEMINAL VESICLES

(49)

(1)

(20)

ATROPHY

1 (2%) [1]

1 (100%) [1]

RUPTURE

1 (100%) [1]

TESTIS

(49)

(56)

(20)

GERM CELL; DEGENERATION

4 (8.2%) [3]

6 (10.7%) [4]

1 (5%) [1]

SEMINIFEROUS TUBULE; SPERMATID RETENTION

3 (5.4%) [2]

4 (20%) [3]

HEMATOPOIETIC SYSTEM

None

INTEGUMENTARY SYSTEM

None

LYMPHOID SYSTEM

None

MUSCULOSKELETAL SYSTEM

None

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**F1 Male : F1 NonParental Male**

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**Treatment Groups (ppm)**

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**0**

**750**

**2500**

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**NERVOUS SYSTEM**

None

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**RESPIRATORY SYSTEM**

None

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**SPECIAL SENSES SYSTEM**

None

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**URINARY SYSTEM**

	<b>0</b>	<b>750</b>	<b>2500</b>
<b>KIDNEYS</b>	(49)	(1)	(20)
PAPILLA; COLLECTING DUCT; DILATION			1 (5%) [1]
PELVIS; RIGHT; DILATION	7 (14.3%) [6]	1 (100%) [1]	3 (15%) [3]
TRANSITIONAL CELL; EPITHELIUM; HYPERPLASIA; FOCAL		1 (100%) [1]	
MINERAL			1 (5%) [1]
NEPHROPATHY, CHRONIC PROGRESSIVE	45 (91.8%) [17]	1 (100%) [1]	20 (100%) [8]

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**F1 Female : F1 NonParent Female**

	Treatment Groups (ppm)		
	0	750	2500
<b>Disposition Summary</b>			
Animals Initially In Study	47	58	27
Early Deaths			
Survivors			
Scheduled sacrifice, terminal (PND 91 - 93)	47	58	27
Number of Animals Examined	47	58	27
Total number litters	17	22	12
<b>ALIMENTARY SYSTEM</b>			
LIVER	(47)	(2)	(27)
HEPATODIAPHRAGMATIC NODULE	1 (2.1%) [1]	1 (50%) [1]	1 (3.7%) [1]
LYMPHOCYTE; INFILTRATION; MULTIFOCAL INFLAMMATION, CHRONIC; ACTIVE, FOCAL	5 (10.6%) [5]		
	1 (2.1%) [1]		
<b>CARDIOVASCULAR SYSTEM</b>			
None			
<b>ENDOCRINE SYSTEM</b>			
PITUITARY GLAND	(47)	(0)	(27)
PARS DISTALIS; CYST	1 (2.1%) [1]		1 (3.7%) [1]
THYROID GLANDS	(47)	(0)	(25)
FOLLICULAR CELL; MINERAL			1 (4%) [1]
<b>GENERAL BODY SYSTEM</b>			
None			

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F1 Female : F1 NonParent Female

	Treatment Groups (ppm)		
	0	750	2500
<b>GENITAL SYSTEM</b>			
CERVIX	(47)	(0)	(26)
ENDOMETRIUM; CYST	1 (2.1%) [1]		
OVARIES	(47)	(2)	(27)
CORPUS LUTEUM; CYST	1 (2.1%) [1]		1 (3.7%) [1]
FOLLICLE; UNILATERAL; CYST		1 (50%) [1]	
UTERUS	(47)	(2)	(27)
OVIDUCT; CYST			1 (3.7%) [1]
SUBSEROA; CYST	4 (8.5%) [4]		
ENDOMETRIUM; HYPERPLASIA; CYSTIC	4 (8.5%) [4]		
VAGINA	(47)	(0)	(27)
MUCIFICATION	5 (10.6%) [3]		
<b>HEMATOPOIETIC SYSTEM</b>			
SPLEEN	(2)	(1)	(0)
<b>INTEGUMENTARY SYSTEM</b>			
None			
<b>LYMPHOID SYSTEM</b>			
None			
<b>MUSCULOSKELETAL SYSTEM</b>			
None			
<b>NERVOUS SYSTEM</b>			
None			
<b>RESPIRATORY SYSTEM</b>			
None			

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**F1 Female : F1 NonParent Female**

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**Treatment Groups (ppm)**

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**0**

**750**

**2500**

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**SPECIAL SENSES SYSTEM**

None

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**URINARY SYSTEM**

KIDNEYS	(47)	(58)	(27)
MINERAL	9 (19.1%) [7] **	44 (75.9%) [19] **	20 (74.1%) [11] **
NEPHROPATHY, CHRONIC PROGRESSIVE	27 (57.4%) [14]	ND	21 (77.8%) [12]

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**F1 Male : F1 Parental Males**

	Treatment Groups (ppm)		
	0	750	2500
<b>Disposition Summary</b>			
Animals Initially In Study	40	44	40
Early Deaths			
Euthanized, moribund			1
Survivors			
Scheduled sacrifice, terminal (PND 218 - 224)	40	44	39
Number of Animals Examined	40	44	40
Total number litters	18	22	15
<b>ALIMENTARY SYSTEM</b>			
LIVER	(40)	(0)	(40)
CLEAR CELL FOCUS	1 (2.5%) [1]		4 (10%) [3]
HEPATODIAPHRAGMATIC NODULE	3 (7.5%) [3]		5 (12.5%) [4]
BILE DUCT; HYPERPLASIA; FOCAL	1 (2.5%) [1]		1 (2.5%) [1]
HYPERTROPHY; DIFFUSE, HEPATOCELLULAR			1 (2.5%) [1]
LYMPHOCYTE; PERIPORTAL; INFILTRATION; MULTIFOCAL	1 (2.5%) [1]		7 (17.5%) [6]
INFLAMMATION, CHRONIC; ACTIVE, FOCAL	3 (7.5%) [3]		
HEPATOCYTE; NECROSIS; FOCAL	1 (2.5%) [1]		2 (5%) [2]
HEPATOCYTE; CENTRIOBULAR; VACUOLATION; CYTOPLASMIC, DIFFUSE			1 (2.5%) [1]
HEPATOCYTE; VACUOLATION; CYTOPLASMIC, FOCAL			1 (2.5%) [1]
<b>CARDIOVASCULAR SYSTEM</b>			
None			



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Species/Strain: Rat/Sprague-Dawley

F1 Male : F1 Parental Males

	Treatment Groups (ppm)		
	0	750	2500
<b>ENDOCRINE SYSTEM</b>			
ADRENAL GLANDS	(40)	(0)	(40)
CORTEX; HYPERTROPHY; FOCAL	1 (2.5%) [1]		1 (2.5%) [1]
CORTEX; VACUOLATION; FOCAL			3 (7.5%) [3]
CORTEX; VACUOLATION, CYTOPLASMIC; DIFFUSE	1 (2.5%) [1]		1 (2.5%) [1]
PITUITARY GLAND	(40)	(0)	(40)
PARS DISTALIS; CYST	3 (7.5%) [3]		1 (2.5%) [1]
THYROID GLANDS	(40)	(0)	(40)
C-CELL; HYPERPLASIA; FOCAL	1 (2.5%) [1]		1 (2.5%) [1]
<b>GENERAL BODY SYSTEM</b>			
None			
<b>GENITAL SYSTEM</b>			
EPIDIDYMIS	(40)	(44)	(40)
DUCT; EXFOLIATED GERM CELL (TOTAL)		5 (11.4%) [5]	4 (10%) [4]
LEVATOR ANI PLUS BULBOCAVERNOSUS MUSCLE	(40)	(0)	(40)
PROSTATE	(40)	(44)	(40)
DORSAL LOBE; EPITHELIUM; ATROPHY			1 (2.5%) [1]
VENTRAL LOBE; ATROPHY	4 (10%) [3] **	10 (22.7%) [8]	35 (87.5%) [15] **
VENTRAL LOBE, INTERSTITIUM; LYMPHOCYTE; INFILTRATION	5 (12.5%) [4]	1 (2.3%) [1]	
SEMINAL VESICLES	(40)	(1)	(40)
ATROPHY			2 (5%) [2]
TESTIS	(40)	(44)	(40)
GERMINAL EPITHELIUM; ATROPHY (TOTAL)	1 (2.5%) [1]		2 (5%) [2]
GERM CELL; DEGENERATION (TOTAL)	2 (5%) [2]	5 (11.4%) [5]	5 (12.5%) [4]
SEMIFEROUS TUBULE; SPERMATID RETENTION		5 (11.4%) [5]	4 (10%) [3]

Experiment Number: R92025B  
 Test Type: RACB  
 Route: Dosing in Feed  
 Species/Strain: Rat/Sprague-Dawley

PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence  
 Test Compound: 4-Methylimidazole  
 CAS Number: 822-36-6

Date Report Requested: 09/04/2018  
 Time Report Requested: 09:32:54  
 Lab: RTI

F1 Male : F1 Parental Males

	Treatment Groups (ppm)		
	0	750	2500
<b>HEMATOPOIETIC SYSTEM</b>			
None			
<b>INTEGUMENTARY SYSTEM</b>			
SKIN	(0)	(2)	(0)
<b>LYMPHOID SYSTEM</b>			
None			
<b>MUSCULOSKELETAL SYSTEM</b>			
None			
<b>NERVOUS SYSTEM</b>			
None			
<b>RESPIRATORY SYSTEM</b>			
None			
<b>SPECIAL SENSES SYSTEM</b>			
None			
<b>URINARY SYSTEM</b>			
KIDNEYS	(40)	(6)	(40)
PELVIS; CONCRETION; FOCAL	6 (15%) [5]		1 (2.5%) [1]
PAPILLA; CYST			1 (2.5%) [1]
PELVIS; DILATION (TOTAL)	9 (22.5%) [8]	4 (66.7%) [3]	1 (2.5%) [1] *
EPITHELIUM; TRANSITIONAL CELL; HYPERPLASIA; FOCAL (TOTAL)	5 (12.5%) [4]	1 (16.7%) [1]	1 (2.5%) [1]
TRANSITIONAL CELL; EPITHELIUM; INFLAMMATION, CHRONIC; ACTIVE, FOCAL	2 (5%) [2]	1 (16.7%) [1]	
MINERAL	3 (7.5%) [3]		5 (12.5%) [2]
NEPHROPATHY, CHRONIC PROGRESSIVE	40 (100%) [18]	6 (100%) [4]	40 (100%) [15]

Experiment Number: R92025B  
 Test Type: RACB  
 Route: Dosing in Feed  
 Species/Strain: Rat/Sprague-Dawley

PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence  
 Test Compound: 4-Methylimidazole  
 CAS Number: 822-36-6

Date Report Requested: 09/04/2018  
 Time Report Requested: 09:32:54  
 Lab: RTI

F1 Female : F1 Parental Females

	Treatment Groups (ppm)		
	0	750	2500
<b>Disposition Summary</b>			
Animals Initially In Study	40	44	40
<b>Early Deaths</b>			
Euthanized, moribund	2	3	6
Found Dead		1	1
Unscheduled Sacrifice	1	1	1
<b>Survivors</b>			
Scheduled sacrifice, terminal (LD 26 - 28, PND 246 - 251)	37	39	32
Number of Animals Examined	40	43	40
Total number litters	19	22	15
<b>ALIMENTARY SYSTEM</b>			
LIVER	(40)	(43)	(40)
SUBCAPSULAR; FIBROSIS; FOCAL		1 (2.3%) [1]	
SUBCAPSULAR; HEMORRHAGE; FOCAL		1 (2.3%) [1]	
HEPATODIAPHRAGMATIC NODULE	1 (2.5%) [1]	1 (2.3%) [1]	2 (5%) [2]
BILE DUCT; HYPERPLASIA; DIFFUSE			1 (2.5%) [1]
LYMPHOCYTE; PERIportal; INFILTRATION; MULTIFOCAL	9 (22.5%) [9]	6 (14%) [6]	5 (12.5%) [3]
INFLAMMATION, CHRONIC; ACTIVE, FOCAL	1 (2.5%) [1]		2 (5%) [2]
CENTRIOLOBULAR; NECROSIS; FOCAL			2 (5%) [2]
HEPATOcyTE; NECROSIS; DIFFUSE			1 (2.5%) [1]
<b>CARDIOVASCULAR SYSTEM</b>			
None			

**Experiment Number:** R92025B  
**Test Type:** RACB  
**Route:** Dosing in Feed  
**Species/Strain:** Rat/Sprague-Dawley

**PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence**  
**Test Compound:** 4-Methylimidazole  
**CAS Number:** 822-36-6

**Date Report Requested:** 09/04/2018  
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**Lab:** RTI

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**F1 Female : F1 Parental Females**

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**Treatment Groups (ppm)**

---

**0**

**750**

**2500**

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**ENDOCRINE SYSTEM**

ADRENAL GLANDS	(40)	(43)	(40)
CORTEX; HYPERTROPHY; FOCAL	1 (2.5%) [1]		1 (2.5%) [1]
LYMPHOCYTE; INFILTRATION; MULTIFOCAL	1 (2.5%) [1]		
CORTEX; VACUOLATION; FOCAL		2 (4.7%) [2]	1 (2.5%) [1]
PITUITARY GLAND	(39)	(43)	(40)
PARS DISTALIS; CYST		1 (2.3%) [1]	
THYROID GLANDS	(40)	(43)	(40)
C-CELL; HYPERPLASIA; FOCAL	5 (12.5%) [5]	3 (7%) [3]	1 (2.5%) [1]
INFLAMMATION; CHRONIC ACTIVE	1 (2.5%) [1]		

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**GENERAL BODY SYSTEM**

None

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Experiment Number: R92025B

PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence

Date Report Requested: 09/04/2018

Test Type: RACB

Test Compound: 4-Methylimidazole

Time Report Requested: 09:32:54

Route: Dosing in Feed

CAS Number: 822-36-6

Lab: RTI

Species/Strain: Rat/Sprague-Dawley

F1 Female : F1 Parental Females

	Treatment Groups (ppm)		
	0	750	2500
<b>GENITAL SYSTEM</b>			
CERVIX	(40)	(42)	(40)
SEROSA; CYST	1 (2.5%) [1]		
OVARIES	(40)	(43)	(40)
CORPUS LUTEUM; CYST (TOTAL)		2 (4.7%) [2]	4 (10%) [4]
FOLLICLE; CYST		4 (9.3%) [4]	
CYST	1 (2.5%) [1]		
PLACENTA	(0)	(1)	(0)
INFLAMMATION, ACUTE; MULTIFOCAL		1 (100%) [1]	
NECROSIS; MULTIFOCAL		1 (100%) [1]	
UTERUS	(40)	(43)	(40)
OVIDUCT; CYST			1 (2.5%) [1]
SUBSEROSA; CYST	1 (2.5%) [1]	2 (4.7%) [2]	2 (5%) [2]
HORN; DECIDUAL ALTERATION		1 (2.3%) [1]	
ENDOMETRIUM; HYPERPLASIA; CYSTIC	6 (15%) [4]		
ENDOMETRIUM; INFLAMMATION; SUPPURATIVE			1 (2.5%) [1]
ENDOMETRIUM; ULCER; FOCAL			1 (2.5%) [1]
VAGINA	(40)	(43)	(40)
MUCIFICATION	3 (7.5%) [3]		
<b>HEMATOPOIETIC SYSTEM</b>			
THYMUS	(40)	(42)	(40)
CORTEX; DECREASED LYMPHOCYTE; DIFFUSE	8 (20%) [7]	10 (23.8%) [9]	9 (22.5%) [8]

**Experiment Number:** R92025B  
**Test Type:** RACB  
**Route:** Dosing in Feed  
**Species/Strain:** Rat/Sprague-Dawley

**PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence**  
**Test Compound:** 4-Methylimidazole  
**CAS Number:** 822-36-6

**Date Report Requested:** 09/04/2018  
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**Lab:** RTI

**F1 Female : F1 Parental Females**

	Treatment Groups (ppm)		
	0	750	2500
<b>INTEGUMENTARY SYSTEM</b>			
MAMMARY GLANDS	(40)	(43)	(40)
INFLAMMATION; SUPPURATIVE INFLAMMATION, ACUTE; FOCAL LACTATION	1 (2.5%) [1]	1 (2.3%) [1]	1 (2.5%) [1]
NECROSIS; FOCAL		1 (2.3%) [1]	
<b>LYMPHOID SYSTEM</b>			
None			
<b>MUSCULOSKELETAL SYSTEM</b>			
None			
<b>NERVOUS SYSTEM</b>			
None			
<b>RESPIRATORY SYSTEM</b>			
None			
<b>SPECIAL SENSES SYSTEM</b>			
None			
<b>URINARY SYSTEM</b>			
KIDNEYS	(40)	(43)	(40)
PELVIS; CONCRETION; FOCAL	9 (22.5%) [8]	1 (2.3%) [1] *	2 (5%) [2]
PAPILLA; CYST		1 (2.3%) [1]	
RENAL TUBULE; EPITHELIUM; HYPERPLASIA; FOCAL			1 (2.5%) [1]
MINERAL	8 (20%) [5] **	21 (48.8%) [14] *	27 (67.5%) [12] **
NEPHROPATHY, CHRONIC PROGRESSIVE	34 (85%) [17]	41 (95.3%) [21]	40 (100%) [15]

**Experiment Number:** R92025B

**Test Type:** RACB

**Route:** Dosing in Feed

**Species/Strain:** Rat/Sprague-Dawley

**PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence**

**Test Compound:** 4-Methylimidazole

**CAS Number:** 822-36-6

**Date Report Requested:** 09/04/2018

**Time Report Requested:** 09:32:54

**Lab:** RTI

**F2 Male**

**Treatment Groups (ppm)**

**0    750    2500**

**Disposition Summary**

**Animals Initially In Study**

**107    132    69**

**Early Deaths**

**Survivors**

**Scheduled sacrifice, terminal (PND 28)**

**107    132    69**

**Number of Animals Examined**

**1**

**Total number litters**

**1**

**ALIMENTARY SYSTEM**

None

**CARDIOVASCULAR SYSTEM**

None

**ENDOCRINE SYSTEM**

None

**GENERAL BODY SYSTEM**

None

**GENITAL SYSTEM**

None

**HEMATOPOIETIC SYSTEM**

None

**INTEGUMENTARY SYSTEM**

None

**Experiment Number:** R92025B  
**Test Type:** RACB  
**Route:** Dosing in Feed  
**Species/Strain:** Rat/Sprague-Dawley

**PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence**  
**Test Compound:** 4-Methylimidazole  
**CAS Number:** 822-36-6

**Date Report Requested:** 09/04/2018  
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**Lab:** RTI

---

F2 Male

---

Treatment Groups (ppm)

---

0

750

2500

---

**LYMPHOID SYSTEM**

None

---

**MUSCULOSKELETAL SYSTEM**

None

---

**NERVOUS SYSTEM**

None

---

**RESPIRATORY SYSTEM**

None

---

**SPECIAL SENSES SYSTEM**

None

---

**URINARY SYSTEM**

None

---



**Experiment Number:** R92025B  
**Test Type:** RACB  
**Route:** Dosing in Feed  
**Species/Strain:** Rat/Sprague-Dawley

**PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence**  
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	F2 Female		
	Treatment Groups (ppm)		
	0	750	2500
<hr/>			
<b>Disposition Summary</b>			
<b>Animals Initially In Study</b>	98	132	76
<b>Early Deaths</b>			
<b>Survivors</b>			
Scheduled sacrifice, terminal (PND 28)	98	132	76
<b>Number of Animals Examined</b>			
<hr/>			
<b>ALIMENTARY SYSTEM</b>			
None			
<hr/>			
<b>CARDIOVASCULAR SYSTEM</b>			
None			
<hr/>			
<b>ENDOCRINE SYSTEM</b>			
None			
<hr/>			
<b>GENERAL BODY SYSTEM</b>			
None			
<hr/>			
<b>GENITAL SYSTEM</b>			
None			
<hr/>			
<b>HEMATOPOIETIC SYSTEM</b>			
None			
<hr/>			
<b>INTEGUMENTARY SYSTEM</b>			
None			
<hr/>			
<b>LYMPHOID SYSTEM</b>			
None			

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**Experiment Number:** R92025B  
**Test Type:** RACB  
**Route:** Dosing in Feed  
**Species/Strain:** Rat/Sprague-Dawley

**PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence**  
**Test Compound:** 4-Methylimidazole  
**CAS Number:** 822-36-6

**Date Report Requested:** 09/04/2018  
**Time Report Requested:** 09:32:54  
**Lab:** RTI

---

**F2 Female**

---

**Treatment Groups (ppm)**

---

**0**

**750**

**2500**

---

**MUSCULOSKELETAL SYSTEM**

None

---

**NERVOUS SYSTEM**

None

---

**RESPIRATORY SYSTEM**

None

---

**SPECIAL SENSES SYSTEM**

None

---

**URINARY SYSTEM**

None

---

**Experiment Number:** R92025B

**PA10R: Statistical Analysis of Non-Neoplastic Lesions with Litter Incidence**

**Date Report Requested:** 09/04/2018

**Test Type:** RACB

**Test Compound:** 4-Methylimidazole

**Time Report Requested:** 09:32:54

**Route:** Dosing in Feed

**CAS Number:** 822-36-6

**Lab:** RTI

**Species/Strain:** Rat/Sprague-Dawley

## LEGEND

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Number of animals examined given for each tissue. If none of the animals examined have the specific lesion then there is a blank for that dose group for that specific lesion. The exception to this is if statistical analysis is performed for a lesion and the control group has no animals with the lesion then a 0 is included for the control group on the table for that lesion.

Number of animals with observation reported with percent incidence in parentheses

Number of litters shown in square brackets for F1 and F2 animals

Statistical analysis for the F0 animals was performed using the Poly-3 trend and pairwise statistics.

Statistical analysis for the F1 and/or F2 animals was performed using a Cochran-Armitage test with a poly-3 adjustment for survival and a Rao-Scott modification for litter effect.

All trend and pairwise p-values are reported as one-sided.

Trend p-values are reported only for those organs that were fully examined in the control group plus two or more other dose groups. For organs that were fully examined in just the control and one other dose group, only the pairwise p-values are reported.

Statistical significance for the control group indicates a significant trend test

Statistical significance for a treatment group indicates a significant pairwise test compared to the vehicle control group

\* Statistically significant at  $P \leq 0.05$

\*\* Statistically significant at  $P \leq 0.01$

Non-pregnant females from the F0 and F1 generations are included in the analysis.

ND - Not Determined

**\*\* END OF REPORT \*\***